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ABSTRAK

Diagnosis dini infeksi Human Immunodeficiency Virus (HIV) dapat mengurangi kebahayaan transmisi. Infeksi akut dapat dideteksi berdasarkan pemeriksaan antigen atau asam ribonukleat (RNA/proviral DNA) HIV. Enzyme Immunoassay (EIA) generasi keempat dapat mendeteksi antigen p24 dan antibodi HIV. Tujuan penelitian adalah mengetahui nilai diagnostik uji HIV generasi keempat di terduga HIV. Penelitian ini merupakan uji diagnostik dengan desain potong lintang. Sampel penelitian adalah semua pasien terduga HIV yang datang ke poliklinik Volunters Counselling and Testing (VCT) RSUP Dr. M. Djamil Padang masa waktu Maret 2015–Maret 2016. Penelitian ini dilakukan untuk menentukan ketepatan diagnostik (kepekaan, kekhasan, nilai peramalan positif, nilai peramalan negatif) uji HIV generasi keempat menggunakan Enzyme Linked Fluorescent Assay (ELFA) terhadap deteksi RNA HIV menggunakan Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) serta dianalisis menggunakan tabel 2×2. Subjek penelitian sebanyak 70 orang terduga HIV terdiri dari 46 laki-laki (65,7%) dan 24 perempuan (34,3%) dengan rerata umur 27,7 tahun. Transmisi HIV terbanyak adalah perilaku heteroseksual (45,7%). Nilai diagnostik uji HIV generasi keempat terhadap RNA HIV didapatkan kepekaan 95%, kekhasan 96%, nilai peramalan positif 97% dan nilai peramalan negatif 92%.

Kata kunci: RNA HIV, uji HIV generasi keempat, uji diagnostik

ABSTRACT

Early diagnosis for Human Immunodeficiency Virus (HIV) infection can reduce the risk of transmission. Acute infection diagnosis based on antigen assay or ribonucleic acid test (RNA/proviral DNA). Enzyme Immunoassay (EIA) fourth generation can detect HIV p24 antigen and antibodies simultaneously. The research objective was to determine the diagnostic value of the fourth-generation HIV testing in HIV suspects. This was a diagnostic test with cross-sectional design, performed on 70 patients with suspected HIV who came to the Volunteers Counselling and Testing clinic (VCT) Dr. M. Djamil Hospital Padang from Maret 2015 to Maret 2016. The study was aimed to measure the diagnostic values (sensitivity, specificity, positive predictive value, negative predictive value) of fourth generation HIV tests with Enzyme Linked Fluorescent Assay (ELFA) against Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) RNA HIV and analyzed using crosstab 2×2. The were 70 subjects, consisting of 46 males (65.7%) and 24 females (34.3%) with a diagnosis of HIV suspects. Mean of age was 27.7 year. Heterosexual was the major transmission of HIV. The sensitivity and specificity of fourth-generation HIV test against HIV RNA were 95% and 96% respectively, and the positive predictive value and negative predictive value were 97 and 92%, respectively.

Key words: Diagnostic test, fourth-generation HIV test, HIV RNA

INTRODUCTION

Risk of Human Immunodeficiency Virus (HIV) transmission rises from 5.5 to 26 times higher during acute infection period or the onset of infection than when symptoms of the disease have already emerged. HIV antibodies actually can be detected 6-12 weeks after the infection (in most people) using the first antibody generation test. However, they can be detected more quickly 3–4 weeks using the third-generation Enzyme Immunoassay (EIA). Acute HIV
Infection can also be detected by examination of Ribonucleic Acid (RNA) or HIV p24 antigen in the blood before antibodies form. The period before the antibodies are formed in acute HIV infection is called window period. P24 antigen can be detected two weeks after exposure to HIV infection for the first time and also during the terminal stage of Acquired Immunodeficiency Syndrome (AIDS). Meanwhile, HIV RNA can be detected 1 week or 4–10 days prior to antigen p24 appears. P24 antigen can also be detected by Enzyme Linked Immunosorbent Assay (ELISA), considered to be more effective and cheaper than HIV RNA with Polymerase Chain Reaction (PCR) method.

Nevertheless, examination of HIV RNA is expensive and not available in all laboratories. Only laboratories that have ELISA facilities can use the fourth-generation HIV test to detect HIV p24 antigen and antibodies simultaneously. There are some advantages of this test, namely reducing the cost of inspection, saving more energy efficiently and screening for HIV infection.

The fourth-generation HIV test, moreover, can detect HIV p24 antigen and HIV antibodies simultaneously based on the principles of a two-step indirect sandwich assay. Early detection of primary infection in seroconversion phase is very helpful in preventing the transmission of HIV to a partner and a child, as well as through blood donation or direct blood contact. The fourth-generation HIV test is also widely used for screening acute HIV infection in blood donors. HIV confirmatory test then is conducted using Western Blot (WB), Immunofluorescent Antibody Assay (IFA) and HIV RNA with Nucleic Acid Amplification Test (NAAT).

HIV infection, furthermore, is a major problem that threatens countries in the world, including Indonesia. Human immunodeficiency virus known in the early 1980s has infected millions of people around the world. Centers for Disease Control and Prevention estimates the 49,000 new HIV cases per year in 2008–2010. Infection of this virus even has caused death of more than 25 million people worldwide and as many as 20–40 million people worldwide have been living with HIV/AIDS. People with HIV, as a result, will decrease the quality of their life in accordance with progression of the disease and emerged clinical manifestations.

A research conducted by Saviell et al. in 2001 reported that the fourth-generation HIV test had a sensitivity of 99.5% and a specificity of 100% in 2847 samples with HIV risk factors. Similarly, a research conducted by Weber et al. in 2002 on 2660 people with low and high risk of HIV infection found that the fourth-generation HIV test had a specificity of 98.1% compared to Reverse Transcriptase-PCR (RT-PCR) (detection of HIV RNA) as the gold standard. A research conducted by Bourlet et al. in 2005 also reported that the fourth-generation HIV test had a sensitivity of 100% and a specificity of 99.8%. However, there is still no research on the fourth-generation HIV test in the Dr. M. Djamil Hospital, Padang.

Human immunodeficiency virus is considered as both an agent causing AIDS and a RNA virus categorized into lenti virus, retrovirus family, which has a molecular weight of 9.7 kb and a spherical shape with a diameter of 100 nm. Structure of HIV can be divided into three main parts, namely outer part of the virus, called as envelope, as well as complexes including the inside of the virus, called as capsid and core. Viral envelope consists of two layers of fatty molecules, called as lipid membranes. The inside surface of the viral lipid envelope is limited by protein matrix (p17) and many cellular proteins. Envelope lipid forms icosahedral sheath together with matrix (p17) and core proteins (p24, p7 and p6). There are two copies of single-strand RNA molecule in the core (see Figure 1).

There are nine genes in RNA HIV strand, consisted of three structural genes, namely gag, pol and env, as well as six gene regulators, namely vif, vpr, vpu, rev, tat and nef. Rev genes play a role in guiding the encoding process of gp41. Rev protein interaction even helps separation of the core RNA transcripts. Vpr gene, moreover, guides the transcription of host cells and infected cells. Nef plays a role in the induction of CD4 receptor downregulation. Vpu genes promote the degradation of CD4 in the endoplasmic reticulum. Vif genes play a role in infectivity of new formed viral particles. The HIV virus, as a result, can be considered...
as an obligate intracellular retrovirus experiencing replication entirely within the host cell.

In addition, HIV infection in the human body begins with gp120 bond on HIV sheath with specific CD4 receptors on the surface of target cells. The main target cells are all cells expressing CD4 receptors, namely astrocytes, microglia, monocyte-macrophages, lymphocytes and dendritics. The interaction of HIV gp120 with CD4 triggers a bond with a target cell. This bond is strengthened with both co-receptors, namely CCR5 and CXCR4. The interaction of HIV gp120 with CD4 triggers a bond with a target cell. This bond is strengthened with both co-receptors, namely CCR5 and CXCR4. Then, the peptides form a complex of P24 antigen can accelerate duration of detection for capture p24 antigen in the serum. Thus, examination are coated with murine monoclonal antibodies to appeared at the beginning of the acute infection components in the blood, p24 antigen, usually antibodies. This test can also detect viral capsid both glycoprotein 160 (gp160) for detecting HIV-1 and gp36 antibodies for detecting HIV-2 antigens in the peripheral region into the target cell membrane. All the particles and genetic information of HIV are carried over into the cytoplasm of a new host cell during the fusion process. RNA genomes moving inside then will form a single strand of DNA helped by reverse transcriptase enzyme, subsequently forming DNA double strand, so interacting with the genomes of the host cell. DNA strand newly formed is called as proviral, subsequently released from the host cell to become new virus.

Dendritic cells, macrophages, and B cells, moreover, are Antigen Precenting Cell (APC) of the immune system involved in the response to HIV. Dendritic cells are able to stimulate specific immune responses and also considered to be important for the initiation of antigen-specific immune response. Dendritic precursors then migrate from the bone marrow to the primary lymphatic organs and also into intestinal submucosal tissue, genitourinary system and respiratory tract. Next, dendritic cells as APC cells will stimulate HIV specific T cells. Dendritic cells that have captured antigen/virus then will migrate to the lymphoid tissue. After that, the antigen stimulates dendritic cells to produce interferon alfa plasmatoid working as antivirus through stimulation of TLR.

The interaction between dendritic cells (as APC) and lymphocytes (B and T cells), furthermore, can be considered as an important effector cell of antigen-specific immune response. Antigens in the peripheral will be captured by dendritic cells, and then processed into small peptides expressed to the cell surface together with costimulatory molecule initiating T cell activation. Next, the peptides form a complex with MHC class I on the surface of dendritic cells, so activating CD8 T-cells and binding to MHC class II to activate CD4 T-cells. CD4 T cells activated into effector cells mediated by cytokines then differentiate into Th1 and Th2 cells. Next, CD4 Th1 cells secrete IL-2 and IFNγ, enhancing function of effectors (CTL, NK cells and macrophages). Th2 cells then produce IL-4, IL-10, IL-5 and IL-6 playing a role in the humoral immune response.

In addition, HIV test consists of two steps, namely screening test and confirmatory test. Screening test is also known as a conventional test, such as enzyme immunoassays (EIA), chemiluminescences assays and another rapid test that has high sensitivity to antibodies and low false-positive results. On the other hand, confirmatory tests include WB, IFA and RNA detection by NAAT that have high specificity.

The fourth-generation enzyme immunoassay actually was first produced in 1985, but is currently widely used because of using a shorter time for diagnosis during window period before antibodies are formed. Meanwhile, the first and second generation can detect IgG antibodies 6–12 weeks for most individuals. Both of these tests, however, can detect HIV antibody, IgG. The first generation test uses viral lysate as the target antigen, while the second generation test uses recombinant proteins for HIV capsid and envelope. The third-generation HIV test, moreover, can detect IgM and IgG antibodies with a sandwich method, which are HIV antibodies from the specimen located between two molecules of antigen, one in a solid phase and the other on enzyme conjugates, such as horseradish peroxidase and alkaline phosphatase.

HIV ribonucleic acid, furthermore, will soon be detected in the blood of individuals 10 days after infected the first time and can be detected by NAAT method in plasma. After 4–10 days, p24 antigen then can be detected using the fourth-generation HIV test. The improvement of p24 antigen is transient since IgM is formed against HIV. Immunoglobulin M can be detected by the third and fourth-generation HIV tests 3–5 days after the p-24 antigen is detected for the first time or 10–13 days after the viral RNA appears. Next, Ig G will be formed and detected by the first and second-generation HIV tests, specifically designed to detect IgG, so the reactive results will appear 18–38 days after the viral RNA detected.

In addition, the fourth-generation EIA test uses both glycoprotein 160 (gp160) for detecting HIV-1 antibodies, and gp36 antibodies for detecting HIV-2 antibodies. This test can also detect viral capsid components in the blood, p24 antigen, usually appeared at the beginning of the acute infection before antibodies are formed. Microtiter wells then are coated with murine monoclonal antibodies to capture p24 antigen in the serum. Thus, examination of P24 antigen can accelerate duration of detection for
acute HIV infection during window period that is to be 2 weeks. EIA test can also improve efficiency and effectiveness of the examination.12,13

This examination, furthermore, applies genomic RNA from clinical specimens. RNA sequences are performed during the preparation of the initial sample and then amplified concurrently with RT-PCR. Next, the number of the target sequence of HIV-1 that appears in each amplification cycle is examined by fluorescence-labeled oligonucleotide probes in Abbott m2000rt tool. Amplification cycle then will increase the fluorescence signal to be detected by Abbott m2000rt tool similar to log concentration of HIV-1 RNA contained in samples.14

Afterwards, the amount of virus in the blood (viremia) of most individuals infected with HIV will decrease from 4 to 6 weeks after the onset of symptoms. After seroconversion, patients clinically will be stable and last for one year. Asymptomatic period is characterized by a low level of virus in plasma, a decline in CD-4 T lymphocytes that can develop into severe immunodeficiency, opportunistic infections, malignancies, and deaths. Production of viral replication then will be balanced with CD-4 T cells infected although the amount of virus in the blood is lower. The amount of virus increases quantitatively is associated with disease progression. The amount of virus in the blood can be measured by quantitative examination of serum p24 antigen, HIV cultures of plasma, or the inspection of viral RNA using amplification or nucleic acid amplification signals.15

METHODS

This research was a diagnostic test with a cross-sectional design. The research population was all patients suspected with HIV who came to the Volunters Counselling and Testing clinic (VCT). Those patients then took a blood test in the Central Laboratory Installation of Dr. M. Djamil Hospital, Padang. Next, the minimum sample size was determined by using a single proportion formula for diagnostic test, about 68 people. Inclusion criteria were patients aged over 18 years and willing to join research (informed consent). Next, examination materials used were in the form of venous blood with EDTA anticoagulant about 3 mL and then stored at –20°C until the tests were done. The fourth-generation HIV tests were carried out using Enzyme Link Fluorescent Assay (ELFA) method, while HIV RNA was examined using Real Time Polymerase Chain Reaction (RT-PCR). Bivariate analysis then was carried out for a diagnostic test using a 2×2 table to fourth-generation HIV tests and HIV RNA examination.

RESULTS AND DISCUSSION

Cross sectional method was applied on the 70 research subjects suspected with HIV who came to the VCT clinic in Dr. M. Djamil Hospital, Padang from September to November 2015. The parameters examined were p24 antigen and both HIV-1 and HIV-2 antibodies with EIA, as well as HIV RNA with RT-PCR. The data obtained then were analyzed using the diagnostic value of 2×2 tables.

Table 1 above showed that the sex of the research subjects was dominated by males as many as 46 people (65.7%) with a lifespan of 18–47 years.

The research subjects then were classified into the group with HIV RNA (+) and the group with HIV RNA (–). The number of the research subjects in the group with HIV RNA (+) was 44 people (62.9%), while with HIV RNA (–) as many as 26 people (37.1%).

Based on the results of the fourth-generation HIV test, there were 42 research subjects (60%) with positive results, one research subject (1.4%) with

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (% )</th>
<th>Mean (SD)</th>
<th>Median (minimmal-maximal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Males</td>
<td>46 (65.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Females</td>
<td>24 (34.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>27.7 (6.9)</td>
<td>29(18–47)</td>
</tr>
<tr>
<td>Transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Heterosexuals</td>
<td>32 (45.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Homosexuals</td>
<td>24 (34.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Intravena drug users</td>
<td>14 (20%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
a false positive, 25 research subjects (35.8%) with negative results, and 2 research subjects (2.8%) with false negative results. Based on the above results, the sensitivity obtained was 0.95 (95%), while the specificity was 0.96 (96%). Positive Predictive Value (NPP) and Negative Predictive Value (NPN) of the fourth-generation HIV test on HIV RNA in those patients with suspected HIV were 0.97 (97%) and 0.92 (92%).

The fourth-generation HIV test, moreover, was conducted on 70 patients with suspected HIV. 46 of whom (65.7%) were males, while 24 of whom (34.3%) were females. Similarly, a research conducted by Ledergerber et al., reported that there were 77% male patients with HIV infection, and 23% female patients. Panel et al., also reported that there were 52% female patients with HIV infection and 48% male patients.

A research conducted by Kilembe et al. in Africa on 123 HIV-positive samples showed that there were 53% females and 47% males. The General Directorate of DG & PL RI in 2014 also reported that in the last 7 years, the number of male patients with HIV infection was higher than females. This is due to risk behaviors for HIV infection more commonly found in men. Meanwhile, in females, it is usually due to transmission from infected couples.

Based on the characteristics of the research subjects, furthermore, the mean age of the research subjects was 29.67 (6.9) years with a lifespan of 18 to 47 years. This result is almost the same as the report of the General Directorate of DG & PL, MoH RI in 2014 that the age range mostly found in the research subjects was in the productive age of 24 to 48 years.

In addition, the most risk factor found in the research subjects was heterosexual (45.7%), including transmitted by infected husbands and commercial sex workers. Another risk factor mostly found in the research subjects was homosexual, in which males are having sex with males (34.3%). The last risk factor commonly found in the research subjects was Injection Drug Users (IDU) as much as 20%. Other risk factors of HIV infection, according to some literatures, are transgender (transvestites), blood transfusions, infected blood product recipients, tattoos, and non-sterile body piercing.

The results of this research, moreover, showed that there were 43 people (61.6%) with the positive results of the fourth-generation HIV test and 27 people (38.6%) with the negative results. In contrast, a previous research conducted by Kilembe et al. in Africa showed that there were only 8 of 34 (23.5%) of patients with acute HIV infection tested for the fourth HIV generation, one of whom was detected for antigens, while seven of whom were detected for HIV antibodies. It may be due to the value of p24 antigen detection limited about 25 pg/mL, as a result, when the value of p24 antigen was very low, it would be difficult to be detected.

The fourth generation EIA uses glycoprotein 160 (gp160) for detecting HIV-1 antibodies and gp36 antibodies for detecting HIV-2. This test can also detect viral capsid components in the blood, namely p24 antigen usually emerging at the beginning of the acute infection before antibodies are formed. Microwells then are coated with murine monoclonal antibodies to capture p24 antigen in the serum. Therefore, P24 antigen test can accelerate time detection for acute HIV infection during window period for 2 weeks. In other words, this test is very useful for the diagnosis of acute HIV infection so that transmission can be prevented. There are actually some advantages of this test, such as conducting in laboratories with ELISA facilities, requiring no special expertise, easy, cost-efficiency and fast compared with examination of HIV RNA using NAAT.

The Food and Drug Administration also has recommended the use of the fourth-HIV generation test to screen for asymptomatic and acute infections of HIV-1 and HIV-2. This test does not require additional examination if the results are negative. Meanwhile, if the results are positive, a confirmatory test on specific antibodies for HIV-1 and HIV-2 is required using either RNA, Western Blot, or IFA. On the other hand, the British Association of Sexual Health and HIV (BASHH) and the British Infection Society has recommended early diagnosis of acute HIV infection using Point of Care Testing (POCT) requiring a confirmatory test to distinguish between HIV-1 and HIV-2.

Based on the results of this research, there was one research subject with a false-positive result. Similarly, a research conducted by Alonso et al. in 2014 reported that there were six research subjects with false-positive results, three of whom were from prospective samples, while three of whom were from screening samples of HIV (+), so the specificity of the fourth-generation HIV test in this research was 99.2%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RNA HIV (+)</th>
<th>RNA HIV (–)</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>The fourth-generation HIV test</td>
<td>42</td>
<td>1</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>26</td>
<td>70</td>
</tr>
</tbody>
</table>
On the other hand, there were two research subjects with false-negative results. These false-negative results may be caused by the levels of p24 antigens not detected by the fourth-generation HIV test. Acute HIV infection can be detected with the fourth-generation HIV test, so it will be very helpful to diagnose HIV when antibodies have not formed yet. Thus, early diagnosis using the fourth-generation HIV test is very important to prevent disease transmission. Based on the results of this research, the sensitivity and specificity of the fourth-generation HIV test on HIV RNA were 0.95 (95%) and 0.96 (96%).

Positive predictive value and negative predictive value obtained in the fourth-generation HIV test were 0.97 (97%) and 0.92 (92%), indicating that 97% of the research subjects were positively infected with HIV, while 92% of the research subjects negatively infected with HIV.

CONCLUSION AND SUGGESTION

This research aimed to analyze the diagnostic value of the fourth-generation HIV test on HIV infection suspects. Based on the results of this research, it may be concluded that the sensitivity, specificity, positive predictive value, and negative predictive value of the fourth-generation HIV test were higher than those of HIV RNA. However, further research with more samples on different populations is still needed.

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